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Division of

Cancer Prevention and Control

1988 Annual Report
Intramural Activities

October 1, 1987
September 30, 1988

U.S. DEPARTMENT
OF HEALTH
AND HUMAN SERVICES

National
Institutes of
Health

National
Cancer
Institute

Bethesda,
Maryland 20892

National Cancer [illegible]

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Table of Contents

Page

Director's Report 1

Cancer Prevention Studies Branch 6

- Objectives 6
- Overview 6
- Accomplishments 6
- Plans 10
- Staff 12
- Bibliography 13

Biometry Branch 17

- Objectives 17
- Overview 17
- Office of the Chief 17
- Biostatistical Methodology and Cancer Control Epidemiology Section 20
- Clinical and Diagnostic Trials Section 26
- Screening Section 33
- Staff 38
- Bibliography 39

Appendix A Intramural Project Summaries (Forms PHS 6040) A1-A17

- The Continued Follow-up of the Breast Cancer Detection Demonstration Project A1
- Linkage of Classical and DNA Markers to the Susceptibility Gene for Breast Cancer A2
- NHANES I Epidemiologic Follow-up Survey: Chemoprevention/Nutrition Aspects A3
- Human Studies of Diet and Nutrition A4
- U.S. Finland Studies of Nutrition and Cancer A5
- Use of Isotretinoin in Prevention of Basal Cell Carcinoma A6
- Nutrition Intervention Studies of Esophageal Cancer In Linxian, China A7
- Cancer Control Objectives and Cancer Mortality Projections A8
- Research in Biostatistical Methodology and Mathematical Modeling A9
- Descriptive Cancer Epidemiology A10
- Cancer in Oriental Populations A11
- Development of Cancer Control Epidemiologic Methods A12
- Statistical Methodology Research A13
- Consultation on Clinical Trials and Other Studies A14
- Design and Analysis of Pharmacokinetic Studies of Selenium A15
- Studies in Cancer Screening A16
- Research in Cancer Screening Methodology and Modeling A17

DIRECTOR'S REPORT

This report describes the intramural research program of the Division of Cancer Prevention and Control (DCPC), one of the four major program divisions of the National Cancer Institute. The mission of DCPC couples basic research on cancer prevention with cancer control research, with the application of technology, and with disease surveillance. The goal of these activities is to achieve significant reductions in cancer incidence, mortality and morbidity, with a concomitant increase in survival. The Division conducts a broad array of cancer control research and application activities which emphasize validation, evaluation, and demonstration. The program ranges from research on prevention using screening and early detection to methods for applying the most effective regimens for cancer treatment, rehabilitation and continuing care. Significant emphasis is given to cancer prevention research. In keeping with an increasing priority on prevention, much effort is being devoted to research on diet, nutrition, and chemoprevention. Intramural research is expanding with the establishment of a new laboratory for nutrition and cancer research.

ORGANIZATION

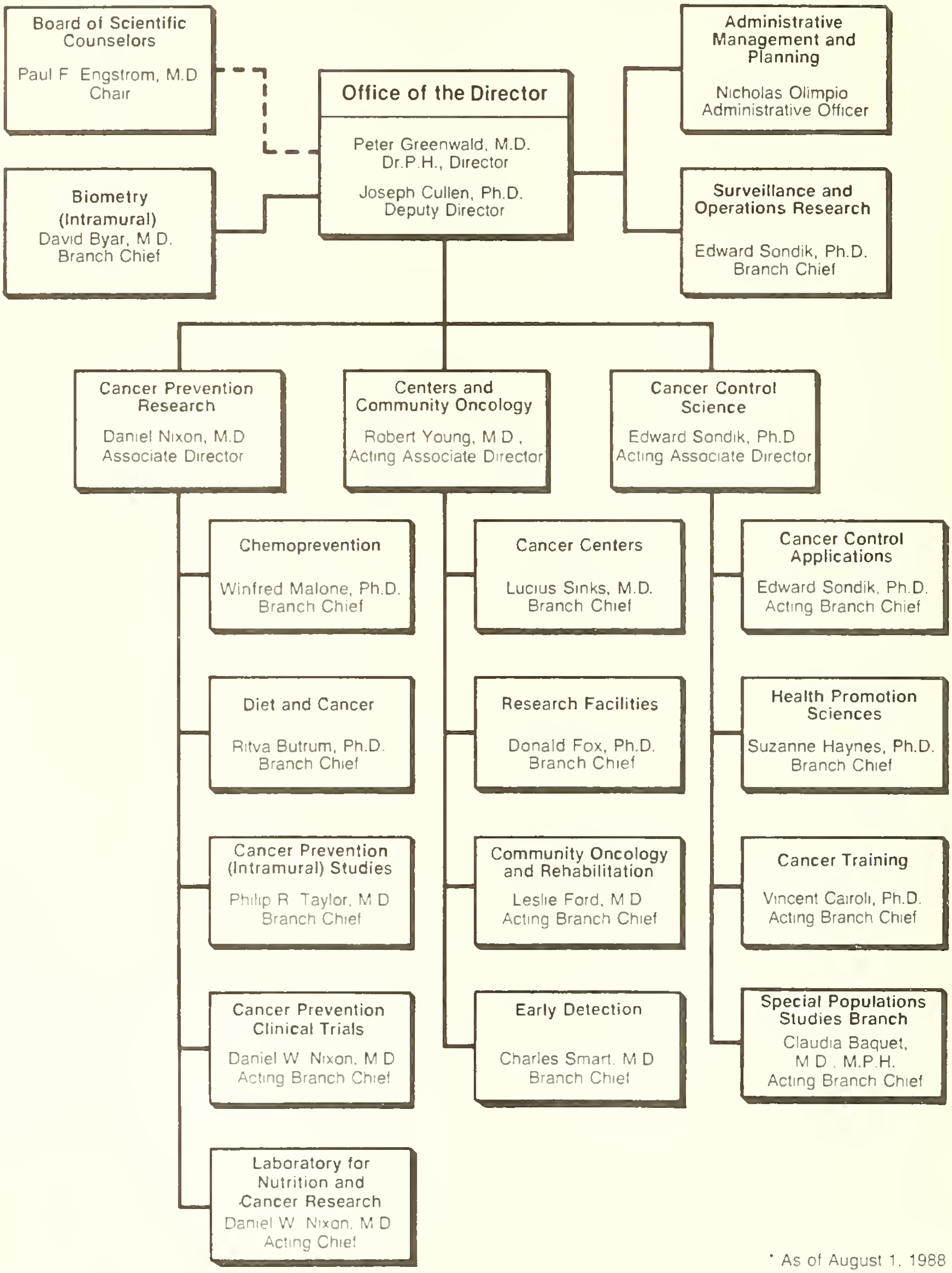
Figure 1 outlines the DCPC organization. The Division consists of three major programs, each led by an Associate Director. The Office of the Division Director provides overall coordination and direction and analytic program support. Each program is described briefly below.

The Cancer Prevention Research Program (CPRP) is charged with planning and supporting both intramural and extramural research in diet, nutrition and cancer and chemoprevention. In addition, this organizational unit serves as the focal point for coordinating diet, nutrition and cancer activities across the NCI divisions. This program houses the Cancer Prevention Studies Branch and a newly-established Laboratory for Nutrition and Cancer Research, two of the three intramural branches in the Division. The Intramural Laboratory for Nutrition and Cancer Research will be located at the Frederick Cancer Research Facility (FCRF) in Frederick, MD.

The Centers and Community Oncology (CCO) Program supports the Nation's network of Cancer Research Centers and community-based clinical research programs. These programs are designed to improve the delivery and application of state-of-the-art cancer treatment, continuing care and rehabilitation. In addition, The CCO is responsible for the integration of cancer center activities with community-based cancer control efforts to develop and disseminate knowledge and technology related to cancer patient management. The Program also conducts research and application activities related to cancer screening and the early detection of cancer. The Community Clinical Oncology Program

FIGURE 1

DCPC ORGANIZATION CHART*


Board of Scientific Counselors
Paul F Engstrom, M.D Chair
Office of the Director
Peter Greenwald, M.D. Dr.P.H., Director
Joseph Cullen, Ph.D. Deputy Director
Administrative Management and Planning
Nicholas Olimpio Administrative Officer
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David Byar, M D. Branch Chief
Surveillance and Operations Research
Edward Sondik, Ph.D. Branch Chief
Cancer Prevention Research
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Centers and Community Oncology
Robert Young, M D , Acting Associate Director
Cancer Control Science
Edward Sondik, Ph.D Acting Associate Director
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Community Oncology and Rehabilitation
Leslie Ford, M D Acting Branch Chief
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Cancer Training
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Special Populations Studies Branch
Claudia Baquet, M D , M.P.H. Acting Branch Chief

* As of August 1, 1988

(CCOP) seeks to link community-based physicians with Cancer Centers and clinical trials research. The CCO also is responsible for the conduct of the Organ Systems Program, which coordinates basic and clinical research on a number of particular cancers, and for the Research Facilities Program designed to support the construction of cancer research facilities throughout the Nation.

The Cancer Control Science Program (CCSP) supports research on ways to effectively transfer cancer control information to the public and to physicians, nurses, and other health professionals. This Program's efforts are directed toward study of a wide variety of cancer control intervention strategies to assess both their impact on populations, and the use of proven cancer control methods. Programs that involve State, local and volunteer health groups, and populations with particularly acute cancer problems, figure prominently in the Program's activities. The Program also directs a number of cancer control resource activities, including the nationwide network of cancer information offices accessible through an 800 telephone number. It is also responsible for the management of the cancer training program for all Divisions of NCI.

The Office of the Director is responsible for the coordination and direction of the Division programs. It includes three branches: the Surveillance and Operations Research Branch (SORB), the Biometry Branch, and the Administrative Management and Planning Branch. The Surveillance and Operations Research Branch includes the Surveillance, Epidemiology, and End Results (SEER) Program and supports the Division in operations research, epidemiology, program evaluation, and computer technology. The Biometry Branch supports intramural research using SEER and other epidemiologic data bases, research in biostatistical methodology, and clinical trials research. The Administrative Management and Planning Branch assists in the management of the Division's budget and administrative matters. The Office of the Director is also responsible for overall coordination of the NCI-wide Smoking, Tobacco, and Cancer Program.

Intramural research is an important component of the programs of the Division of Cancer Prevention and Control. The presence of an intramural program provides extramural program directors ready access to technical expertise relevant to scientific decisions. Moreover, an intramural program brings to the Division the resources to take advantage of a number of research and cancer control opportunities unique to, or important to, the Federal Government including international or interagency collaborations and rapid access to specific high risk target populations. The program also enables methodological research to be pursued that is fundamental to developing the technical approach underlying many large-scale cancer control research projects. Traditionally at NIH, a strong intramural program has enhanced extramural support in its research area. Our new intramural nutrition research program is anticipated to stimulate the extramural nutrition research community in this high-priority endeavor.

Within DCPC, the intramural research program is conducted through the Cancer Prevention Studies Branch (CPSB), the Biometry Branch, and a new intramural Laboratory for Nutrition and Cancer Research, the first phase of which is nearly complete. The Cancer Prevention Studies Branch, located in the Cancer Prevention Research Program, contributes to the cancer control process by conducting controlled intervention studies. Intervention studies serve the dual purposes of confirming hypotheses about cancer etiology and effecting cancer control, and act as a bridge between these two types of research efforts. The CPSB conducts intramural research in the areas of diet, nutrition and cancer, cancer chemoprevention, occupational cancer studies, and other cancer prevention strategies directed toward methods development and their application to reduce human cancer risk. The Biometry Branch, located in the Office of the Director, plans epidemiologic methodology and in mathematical modeling of processes relevant to cancer prevention and control activities. The Biometry Branch also provides consultation on statistical methodology and study design. The Laboratory for Nutrition and Cancer Research will plan, develop, implement and conduct intramural research on nutrition and diet as they relate to the prevention of cancer in humans. The Laboratory will also contribute scientific back-up to the National Cancer Institute's programs in research on diet, nutrition and cancer, and serves as a focal point for new information pertaining to nutrition research. The major areas of research will include basic nutrition science and clinical/metabolic nutrition studies. Laboratory space has been acquired at FCRF and a modest amount of space has been committed in the NIH Clinical Center to begin some metabolic research in humans. A Laboratory Chief for the Nutrition Research Laboratory is expected to be named by October. Beginning in FY 1989, Architectural and Engineering design will begin on a new laboratory for completion in 1990-91.

One of the factors behind the strong research programs at the National Institutes of Health (NIH) is the use of peer review in the development and evaluation of research programs. The need for peer review applies both to intramural as well as extramural programs. Committees of outstanding scientists representing the various disciplines involved in the intramural research program periodically review the direction and progress of the research program and staff. All of the intramural program is subject to the same critical review including the concept of new research ideas prior to their implementation.

The committees that review the intramural research address the breadth and depth of each project and its relation to the Division mission. Critiques also address the quality, progress, future directions and an assessment of resources and staff development. Recommendations made at review are monitored and the impact of their outcomes are assessed in subsequent site visits by the Board of Scientific Counselors and its appropriate subcommittees.

Traditionally at NIH, a strong intramural program has provided leadership and focus to stimulate the scientific community in general to respond to important problems and to complement the research needs in a given area. Research in Cancer Control is no exception to that tradition and a vigorous, high-quality, peer-reviewed intramural program is anticipated to provide the necessary leadership.

Division Director:	Peter Greenwald, M.D., Dr.P.H.
Deputy Director:	Joseph W. Cullen, Ph.D.

Cancer Prevention Studies Branch

OBJECTIVE

The overall objective of the Cancer Prevention Studies Branch (CPSB) is to identify, develop, and test hypotheses relevant to cancer control.

OVERVIEW

The CPSB conducts intramural research in the areas of diet, nutrition and cancer, genetics and cancer, cancer chemoprevention, and other cancer prevention strategies aimed at lowering human cancer risk. This specifically involves:

1. Analysis of existing dietary, genetic, and lifestyle data in relation to cancer, and the development of new studies and data resources to evaluate these relationships;

2. Conducting clinical studies of the metabolic effects of dietary changes in humans; and determining the safety, toxicity, pharmacokinetics, bioavailability, and mechanisms of action of macro- and micronutrients;

3. Conducting intervention trials designed to test the effect of nutritional and chemopreventive agents in reducing cancer risk; and

4. Conducting applied research in the areas of statistical and epidemiologic methods.

ACCOMPLISHMENTS

The Branch has initiated a number of intramural projects in 3 broad areas, including etiologic studies, clinical nutrition studies, and prevention trials. These projects represent collaborative efforts in investigating dietary, nutritional, and constitutional factors relating to cancer prevention. The following is a brief summary of the eight currently active major intramural projects, all of which will continue through and beyond FY 88.

Etiologic Studies

The Continued Follow-up of the Breast Cancer Detection and Demonstration Project (BCDDP) (Z01 CN 00143 CPSB)

The BCDDP screening program began in 1973 in 29 centers in 27 widely dispersed geographic areas of the United States. Initial screening was completed on over 280,000 women over a 2-year period. From the original 280,000 participants in the screening phase of the BCDDP, approximately 64,000 were selected for 5 years of long-term follow-up (LTF) beginning in 1978, to assess the biology and natural history of breast disease, and to test hypotheses relating to detection, etiology, and survival. Those selected for LTF included all breast cancer cases found during the screening phase, all benign breast disease cases, all those recommended for biopsy, and a sample of "normals". The LTF data base will facilitate the exploration of important questions regarding the etiology and natural history of breast cancer. The size of the subcohorts and breadth of data available on them makes this population unique. The large number of cases of both breast cancer and benign breast disease with histologic information available should allow particularly useful analyses of several risk factors in relation to these conditions.

The first 5 years of LTF was completed September 1986 in all centers, and a further continued follow-up of the LTF subcohorts has begun.

This study is being conducted jointly by the Environmental Epidemiology Branch of the Division of Cancer Etiology and the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control.

Linkage of Classical and DNA Markers to the Susceptibility Gene for Breast Cancer in High Risk-Families (Z01 CN 00145 CPSB)

The overall goal of this project is to further an understanding of the genetic, environmental, and cultural influences that are involved in the etiology of human breast cancer. The specific aim is to test for genetic linkage between a large array of discrete, polymorphic genetic markers and the gene(s) for breast cancer in family data. The ultimate goal is to localize a gene or genes that predispose women in high-risk families to breast cancer. A sample of women with a strong family history of breast cancer who participated in the Breast Cancer Detection Demonstration Project (BCDDP) have been contacted and pedigree, vital status, health history, and epidemiological data collected from them and their family members. Thirteen families whose pedigree structure were the most informative for use in linkage analysis studies were selected. Blood has been collected from most of these families and analyzed for the presence of a number of genetic markers, including protein markers, oncogenic sequences, and restriction fragment length polymorphisms (RFLPs). Linkage analysis is underway on these high-risk BCDDP families.

This project started in September 1986 and will continue for 3 years.

NHANES I Epidemiologic Follow-up Survey: Chemoprevention/Nutrition Aspects (Z01 CN 00104 CPSB)

The purpose of the NHANES (National Health and Nutrition Examination Survey) Initial Epidemiologic Follow-up Survey was to conduct a longitudinal study of 14,407 adults originally surveyed in 1971-75, to investigate subsequent health and mortality outcome. Respondents were traced and re-examined. Information was obtained from hospital records, the National Death Index, and death certificates. The NHANES Initial Follow-up Survey was completed in 1984. The purpose of this intramural project is to examine the relation of chemopreventive, nutritional, and constitutional factors to cancer in the very large, representative population which NHANES offers. It provides an opportunity to examine these factors and potentially confounding or modifying factors in a prospective fashion, and to examine the effectiveness of dietary agents which are currently of great interest for cancer prevention. The relation of baseline vitamin use, biochemical or nutritional measures, and subsequent health status will be examined. A Continued Follow-up of the elderly ($\geq$ 75 years old) in this cohort was conducted in 1985-86, while the entire cohort was followed up in 1986-87.

Clinical Nutrition Studies

Human Studies of Diet and Nutrition (Z01 CN 00101 CPSB)

The role of dietary factors in cancer prevention has been assessed in animal experiments, in human epidemiologic studies, and most recently, in prevention trials. For many of these agents, however, information is incomplete concerning their safety, toxicity, dose, form, bioavailability, pharmacokinetics, and mechanisms of action. To further define these parameters in humans, a cooperative research effort between the Beltsville Human Nutrition Research Center (BHNRC), U.S. Department of Agriculture, and the CPSB, DCPC, is being conducted. Initial efforts have focused on three nutrients which have shown the most promise for cancer prevention -- selenium, fat, and beta-carotene.

A study of the kinetics of a single, oral dose of two forms of selenium in the fasting and non-fasting state was conducted in the first year. Current activities include evaluations of the safety/toxicity of selenium and form of ingestion among persons residing in seleniferous areas.

Studies examining the metabolic effects of changes in dietary fat and fiber have been conducted separately in premenopausal women, postmenopausal women, and men. These dietary changes are being related primarily to serum lipids, hormonal status, bile acid metabolism, and fecal mutagenicity.

Beta-carotene studies are examining the plasma carotenoid response to single and long-term ingestion of beta-carotene from either a capsule or from selected vegetables.

Prevention Trials

U.S.-Finland Studies of Nutrition and Cancer (Z01 CN 00100 CPSB)

The important relationship of diet and nutrition in the development of cancer has become well known through various research efforts. Laboratory studies have shown cancer inhibitory function for various natural and synthetic nutrients in various models, which have been corroborated by human epidemiologic studies of nutrient intake, tissue levels, and cancer incidence. Vitamin A, beta-carotene, and selenium have been strongly implicated for their cancer preventive potential, with sufficient evidence for these substances to warrant their use in prevention trials. In addition, the roles of other nutrients in cancer cause and prevention (e.g., dietary fats and fiber) require further investigation.

The objectives of this cooperative project with the government of Finland are: 1) to determine if either beta-carotene or alpha-tocopherol supplementation is effective in preventing lung cancer in smokers; 2) to better assess the role of fats, selenium, and vitamins A, E, and C in breast cancer development; 3) to evaluate the relation of intake of various nutrients to subsequent cancer.

The project includes three studies. The first is a 5-year, randomized, double-blind, placebo-controlled, 2 x 2 factorial prevention trial of daily beta-carotene (20 mg daily) and alpha-tocopherol (50 mg daily) among smokers at high-risk for lung cancer. The difference in lung cancer incidence between intervention groups will be determined. The second is a breast cancer case-control study of fats, total calories, selenium, and vitamins A, E, and C. The role of various anthropometric measurements as well as genetic markers for breast cancer will be explored. The third project will be a comparison of nutrient intakes in cases and references subjects identified from an existing large cohort with prediagnostic baseline dietary histories. Associations between various dietary components and several cancers will be assessed. Several pilot studies have been completed to date, data collection has been completed for the breast cancer study, and recruitment has been completed for the prevention trial, with over 28,000 men entered.

Use of Isotretinoin in Prevention of Basal Cell Carcinoma (Z01 CN 00103 CPSB)

This study is a 5-year, randomized, double-blind prevention trial designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinomas in a high-risk population, and to examine possible side effects associated with long-term administration of low doses of isotretinoin. 981 subjects were entered into the study over a 36-month period at eight participating clinical centers located around the country. At each center, subjects were randomly allocated to intervention (10 mg/day) or control (placebo) groups during the recruitment period which concluded in June 1987.

Vitamin A and its analogs, collectively known as retinoids, have been actively studied for several years in relation to their requirements in normal physiology and health, as well as for their potential in prevention of human disease. This vitamin is necessary for the differentiation of epithelial cells and is essential for the development and function of growth, reproduction, and vision. Deprivation or deficiency of vitamin A promotes tissue metaplasia and neoplasia in various animal and organ culture models. Supplementation with retinoids can reverse these changes and restore functions of cell growth and differentiation in various cell lines.

Laboratory experiments have shown that retinoids administered to animals can prevent chemical carcinogenesis. Since in most of the experiments animals were administered retinoids after their exposure to the carcinogen, the prophylactic effect of the retinoids is believed to be in the post-initiation phase, i.e., during promotion of carcinogenesis. In addition, several epidemiologic studies have shown an association of low dietary intake or serum levels of vitamin A with increased risk of cancer, notably lung cancer and other tumors of epithelial origin. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinomas for 4 years in patients at high risk of developing new tumors.

Nutrition Intervention Studies of Esophageal Cancer in Linxian, China (Z01 CN 00112 CPSB)

The purpose of this project is to conduct two intervention trials using multiple vitamin-mineral supplements to evaluate the relation between such supplements and esophageal cancer mortality. One trial is being conducted in patients diagnosed with esophageal dysplasia (n = 3,400) and the other in the general population (n = 30,000). Participants for the dysplasia trial were screened and recruited in the Summer of 1984 and distribution of active pills initiated in May 1985. For the general population trial, screening/recruitment was accomplished during the Summer 1985, and active pill distribution started in March 1986. The studies will evaluate the effect of these supplements on regression/ progression of esophageal dysplasia, total cancer incidence, total cancer mortality, and total mortality. These two studies are being conducted in Linxian (Henan Province) in the People's Republic of China (PRC). Linxian, a rural county with population of 800,000, was selected because it has the highest rate of esophageal cancer in the world, and because there is suspicion that the population's chronic deficiencies of multiple nutrients may be etiologically involved.

This study is being conducted jointly by the Biostatistics Branch of the Division of Cancer Etiology and the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control at the NCI in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences.

PLANS

The potential role of alcohol consumption in the etiology of breast cancer has been prominent in several recent studies and is particularly important because, unlike other major breast cancer risk factors such as family history, it can be modified. This hypothesis requires verification in other populations with attention to questions about amount and type of alcohol consumed, the time of life drinking occurred, and the potential mechanism of action. Studies are being designed to address these questions.

Several studies have now shown that increased body size is associated with an increased risk for cancer, particularly cancer of the breast. This result suggests a role for remote nutrition, particularly total caloric intake during youth, in carcinogenesis. Studies are being planned in both animals and humans to confirm these observations and identify a mechanism of action.

Studies of the role of genetics in the etiology of esophageal cancer are planned, including molecular genetic studies.

New clinical nutrition studies are being planned. Such studies will evaluate: the effects of alcohol consumption on hormonal status; kinetics studies of the ingestion of various forms of vitamin C, both in foods and supplements; the influence of omega-3 fatty acids on the prostaglandin system; and other newly identified natural substances with potential chemopreventive action.

Experimental studies of cancer such as the ongoing nutrition intervention studies represent a powerful approach in testing the diet-cancer hypothesis. Such studies, however, are long and expensive, typically requiring 5 or more years for completion. The use of intermediate markers is a new and exciting approach in the study of carcinogenesis. The major advantage to studies of intermediate endpoints is that, relative to trials using cancer as the endpoint, they can be conducted with smaller numbers of subjects over shorter periods of time. To date, only a few nutrition intervention studies using intermediate markers have been reported, and none have been conducted in the context of a study with cancer as its final endpoint. Nesting studies of intermediate markers within ongoing intervention studies in which cancer is the final endpoint represents the ideal circumstance in which to determine the relation of the intervention agent to both the intermediate and final endpoints. We are currently examining a number of intermediate endpoints in clinical trial participants. Evaluations include studies of cytologic and histologic change, studies of cell proliferation and differentiation, and examination of cellular

DNA content.

The ongoing prevention trials will continue. The feasibility study for a lung cancer intervention study among Yunnan tin miners has been evaluated and plans for a full trial are being developed. Other plans are being made for a trial which will use both diet modification and nutrient supplementation to prevent recurrence of colonic polyps.

STAFF

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Cancer Prevention Studies Branch

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BIOMETRY BRANCH

OBJECTIVES

The overall objectives of the Biometry Branch are summarized in the functional statement:

- "Plans and conducts independent and cooperative research studies concerning cancer epidemiology, prevention, screening, diagnosis, treatment, and control using methods of mathematical and analytic statistics;

- plans and conducts independent and collaborative studies in biostatistical and epidemiologic methodology and in mathematical modeling of processes relevant to cancer prevention and control activities;

- provides consultation and review of proposed projects concerning biostatistical methodology and study design to staff of the Division and to investigators in other divisions of the NCI and outside;

- provides expertise in statistics and biometry to management and scientific decision-making meetings within the NCI and outside."

OVERVIEW

The work of the Branch is conducted via three Sections and by the Office of the Chief. The principal projects underway in each of these four organizational units will be described separately. The functional statements for each of the three sections will precede the description of their projects. Projects that involve collaboration across Sections or with the Office of the Chief have been placed arbitrarily in this report to avoid duplication.

OFFICE OF THE CHIEF

Cancer Control Objectives and Cancer Mortality Projections (Z01 CN 00142-04 BB)

A comprehensive interactive Fortran program which projects cancer mortality and incidence figures (numbers and rates) from 1980 through 2020 serves as a focus for several projects within the Division. The program incorporates two different survival models (Weibull and mixed exponential), over 40 cancer sites, the ability to begin with or without prevalent cases, temporal trends in underlying cancer incidence and in mortality from other causes, three possible types of intervention (primary prevention, screening, and treatment), age adjustment, calculation of annual incidence and mortality statistics, and comparison of these statistics under changing conditions of trends and interventions. The Biometry Branch staff work closely with SORB and other DCPC staff. Work during the past year has included continued refinement of the computer model, updating the basic underlying database, projections of rates for several industrial states in the U.S., and analysis of breast cancer.

The Women's Health Trial and Fatty Acid Profiles as a Marker for a Low Fat Diet

The Women's Health Trial was to have been a large-scale randomized cancer prevention study designed to test whether or not a low fat diet would reduce the incidence of breast cancer in women at increased risk. Beginning in late 1985, the Biometry Branch Chief took on major responsibility as a scientific advisor to this trial, serving on the Steering Committee and working very closely with the Project Officer in the day-to-day decisions involved in managing the pilot phase of this large-scale effort. Although the result of the feasibility studies clearly indicated that large numbers of women could be recruited to such a project and that the required change in dietary fat could be achieved, in January of 1988 the DCPC Board of Scientific Counselors voted that this trial should not proceed as designed into full-scale implementation. Questions were raised about the underlying rationale for the trial and about the magnitude of the effect that one could reasonably expect to see, and there was concern about whether or not the study subjects were reporting their fat intake accurately. At various stages of review it became clear that the absence of a biochemical marker for compliance to the diet was a serious draw-back in mounting a scientifically convincing project.

As noted in last year's Annual Report, the NCI-USDA Feeding Study was designed to answer some specific questions raised in the pilot phase of the Women's Health Trial. Forty-nine women were fed two experimental diets having 20% of total calories as fat. Analysis of fatty acid profiles in cholesteryl esters and phospholipids for these women have shown that changes in the composition of the fatty acids may serve as a surprisingly accurate marker for a low fat diet. In the phase-out of the Women's Health Trial, all participants were asked to complete a food frequency questionnaire and provide a blood sample at their exit visit. Eighty pairs of baseline and exit visit blood samples, 40 from the control group and 40 from the intervention group, are being analyzed for fatty acid profiles in order to see whether the results of the NCI-USDA Feeding Study can be confirmed, whether predictive indices based on the fatty acid profiles can be calibrated to estimate the percentage of fat in a diet, and to provide some information about compliance in the early phase of the Women's Health Trial before its termination. Several staff members from the Biometry Branch are working intensively on this problem because this information will be helpful in the design of future studies of dietary modification.

Analysis of Mammary Carcinogenesis Experiments in Rodents Related to the Effects of Fat

It has recently been suggested that the effect of dietary fat on mammary carcinogenesis in mice and rats can be explained by the effects of calories and that there is not any specific fat effect. Because of dissatisfaction with the published overviews on this subject, a detailed re-analysis and synthesis of many experimental reports has been undertaken to re-examine this question. Thus far a portion of the mouse experiments had been analyzed using regression techniques for combining information over a number of experiments. The results of this analysis do not support the view that the effect of fat intake in promoting tumors is entirely due to an increase in energy intake. The analysis of separate tumor types suggests, however, that this conclusion may be tumor specific. It is upheld in the mammary tumor experiments in which the effect of fat is estimated to be one-third of the effect of calories, but not supported in skin tumor experiments in which the separate effect of fat is negligible. A systematic search of the literature is underway to identify all further mouse experiments and in addition experiments in rats will be analyzed separately. This work has high priority because it will provide sound scientific data relating to the cancer-fat hypothesis. It is important to know whether or not the view taken by some critics of the Women's Health Trial concerning the implications of animal carcinogenesis experiments are correct or not because it is likely that further cancer prevention trials involving fat reduction will be proposed.

Workshop on Errors-in-Variables

The statistical problem of errors-in-variables arises when the independent variables in a regression model are subject to appreciable random error and thus may not be considered as fixed quantities as they are in traditional analyses. This problem takes on great importance in assessing dietary information in case control and prospective epidemiologic studies because reported dietary intake assessed by food frequency questionnaires, dietary records, or 24 hour recall are subject to very large random errors. Use of ordinary statistical methods for analyzing such data can lead to marked underestimates of the true effects and can even lead to mis-estimation of the direction of any effects. Until quite recently there has been very little work on this problem in the field of biostatistics and standard textbooks have little to say on the subject. Because of the great importance of this statistical problem to the proper interpretation of epidemiologic data necessary for designing cancer prevention studies, the Chief of the Biometry Branch in collaboration with Dr. Mitchell Gail, Chief of the Epidemiology Methods Section of the Division of Cancer Etiology, organized a one and a half day workshop entirely devoted to this subject which was held in October 1987. Seventeen biostatistical methodologists who are actively working on errors-in-variables presented their ideas and techniques for analyzing such data and about 100 other statisticians and epidemiologists, mostly from NIH, attended. The proceedings of this workshop will be published in the journal *Statistics in Medicine*. All papers have now been received and are in various stages of review and revision.

BIOSTATISTICAL METHODOLOGY AND CANCER CONTROL EPIDEMIOLOGY SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Plans and conducts independent and collaborative research concerning biostatistical and epidemiologic methodology related to cancer prevention and control;

- conducts or collaborates in the design and implementation of studies aimed at developing, refining, and testing hypotheses relating to applied cancer prevention and control, community oncology, and diffusion and adaptation of effective prevention, control, and treatment technologies;

- plans and conducts independent and cooperative studies into the theory and analysis of cancer prevention and control;

- provides statistical consultation both within and outside the NCI to researchers concerned with problems related to Section responsibilities and staff expertise."

Research in Biostatistical Methodology and Mathematical Modeling
(Z01 CN 00121-04 BB)

Non-Identifiability Problem in Age-Period-Cohort Modeling

Age-period-cohort models applied to a table of counts of cancer cases or deaths by age, calendar period, and birth cohort are often used to analyze cancer incidence/mortality trends. These models suffer from being non-identifiable in the sense that the linear components of the calendar period and birth cohort trends cannot be uniquely estimated. Robertson and Boyle have recently proposed a new method which claims to solve this non-identifiability problem. Our research has shown, however, that the Robertson-Boyle approach gives biased estimates and we have developed a method using linear interpolation which eliminates most of the bias.

Mathematical Models of Drug Resistance to Anti-Tumor Agents

This research expands the simple time-homogeneous Goldie-Coldman model for resistance of tumor cells to the cell-killing effect of chemotherapy. The model is extended in two ways: (1) to include the more general situation of time-varying stochastic birth, death, and mutation of tumor cells; and (2) to include some kind of treatment, such as immunostimulation, which kills cells resistant to conventional chemotherapy so that a "cure" is possible. Formulas for the mean, variance, and probability distribution of the number of sensitive and resistant cells as a function of time have been derived to predict the effect of different schedules under situations involving different time patterns of cellular birth, death, mutation to resistance, and the cell-killing effect of treatment. A further extension to multiple kinds of resistance is planned.

Models to Estimate the Effect of First Pregnancy on Breast Cancer

Epidemiologic and experimental evidence point to hormones as playing an important role in the pathogenesis of breast cancer. Women with an early menarche and women with a late menopause have been found to exhibit a high risk of breast cancer. Pregnancy has also been found to be an important factor in both human breast cancer and mammary cancer induced in experimental animals. Women who have had their first full-term pregnancy at a young age are at lower breast cancer risk than are women who had their first child at a later age. The risk for nulliparous women falls between these two extremes. Experimental studies have indicated that the first full-term pregnancy produces two competing effects on the development of mammary cancer in rats, one protective and one which increases risk. The purpose of this project is to apply the Moolgavkar-Knudson two-stage carcinogenesis model to the results of the BCDDP case-control study of breast cancer in order to estimate the relative magnitudes of these competing effects in humans.

Errors in Variables for General Linear Models

Many biomedical studies involve measurements which are made with error. For example, in the analysis of cancer risk associated with diet, questionnaire studies can measure current and past dietary components only with sizeable error. Most statistical analysis techniques neglect these measurement errors and therefore give biased estimates of the diet-cancer association. The purpose of this research is to develop a General Linear Model (GLIM) regression method for randomized trials which adjusts for this error in measured covariates to give an unbiased estimate of the treatment effect. A computer program is being developed to estimate the regression coefficients and magnitude of the measurement error variability. Initial testing of its convergence properties is being carried out by simulating Poisson data.

Evaluation of Additive versus Multiplicative Relative Risk Model

The results of many epidemiologic studies of exposure to two or more carcinogens have been used to make inferences regarding their joint mode of action on the basis of whether an additive or multiplicative relative risk model fits the data. The usual inference is that a multiplicative model implies the two carcinogens act at different stages while an additive model implies they act at the same stage. Our research on this project shows this inferential rule is too simplistic and that the time patterns of the two carcinogenic exposures must be taken into account. We show that exposure to two carcinogens acting at two different stages of a multistage carcinogenic process, the first and the penultimate, can produce relative risk relationships which are additive, multiplicative, between additive and multiplicative, or even greater than multiplicative depending upon the exposure timing.

Unbalanced Repeated Measures Linear Regression Procedure

Many sets of data involve repeated measures, e.g. blood samples from the same individual being measured at different times, in which the experimental design is unbalanced, e.g. individuals sometimes skip their scheduled sample collection. No statistical procedure to correctly analyze data such as this is available in the commonly used packages, SAS, BMDP, or SPSS. A recent paper by Jennrich and Schluchter developed the computational formulas for maximum likelihood normal theory regression in this situation. A computer program using these formulas is being developed which will allow examination of a variety of correlation structures for the repeated measures. An easy to use SAS procedure based on this computer program will also be developed.

Descriptive Cancer Epidemiology (Z01 CN 00115-05 BB)

Monitoring Time Trends in Kidney Cancer Incidence

Kidney cancer incidence rates in the U.S. have increased significantly over time. The white population in the upper north central area of the country is at high risk for this disease. Ethnicity accounts for a major part of this geographic pattern; descendants of German, Scandinavian and Russian origin are especially susceptible to kidney cancer. Iowa is mainly composed of whites and has a relatively large population of German descendants. The aim of this project is to find out whether an increase in kidney cancer incidence can be detected in the various counties of this state and if it can be correlated to ethnicity. The analysis involves monitoring the rate of disease in separate counties using the sets and cusum techniques.

Survival Patterns for Malignant Mesothelioma

In conjunction with investigators in the Environmental Epidemiology Branch, survival analyses of 1,475 cases of malignant mesothelioma ascertained through the SEER Program for the years 1973-1984 were completed. Women below the age of 50 had unusually long survival, even after adjustment for the effects of other prognostic variables in the Cox regression model. The findings suggest that age, gender, and stage of disease should be carefully considered in designing and analyzing clinical trials for people with mesothelioma. The results also offer weak support for the hypothesis that asbestos exposed cases of mesothelioma have worse prognosis than other cases.

Age-Period-Cohort Analysis of Lung Cancer Mortality Among World War I Veterans of Known Smoking Status

A study of lung cancer mortality among nearly 294,000 World War I veterans of known smoking status is being done in collaboration with investigators in the Epidemiology and Biostatistics Program. Previous studies of temporal patterns in U.S. lung cancer mortality have been done without specific reference to smoking and have related these patterns to secular changes in tobacco use. An age-period-cohort Poisson regression model will be used to evaluate the effects of age at death, period of death, and cohort of birth on lung cancer mortality rates within different smoking groups in order to clarify the secular trends in this disease.

Morbidity Among Long-Term Survivors of Childhood Cancer and Their Offspring

This retrospective cohort study, done in collaboration with investigators in the Division of Cancer Etiology, was designed to detect the effects of cancer and its treatment on childhood patients who survived to adulthood, as well as any effects that might have been transmitted to their offspring. Cases selected from five U.S. cancer registries were patients under age 20 with a histologically confirmed malignant neoplasm or brain tumor diagnosed during 1945-1974. Patients must have survived at least 5 years and reached the age of 21 years by December 31, 1979. Up to two sibling controls were selected for each case with sequential priority given to full blood relationship, same sex, closest in age. Interviewer-administered questionnaires were obtained for 2,283 (91 percent) cases and 3,270 (91 percent) controls.

In a study of adverse pregnancy outcomes among female survivors of Wilms' tumor, the risk compared to like-sexed sibling controls was estimated using regression models for binomial data adapted to account for the lack of independence in outcomes for the same individual. Excess risks of miscarriage and low birth weight babies were detected.

For those who survive cancer diagnosed at a young age, marriage reflects a sense of well-being and optimism about recovery and future life. In multivariate analysis using a proportional hazards model, only survivors of central nervous system tumors were found to have substantial and statistically significant marriage deficits compared to their sibling controls.

The level of education attained by these survivors was investigated and compared to that of their sibling controls. Survivors of central nervous system tumors were significantly less likely than controls to complete eighth grade or, if they completed high school, to enter college. No differences in educational achievement were found for survivors of other types of cancer.

Cancer in Oriental Populations (Z01 CN 00113-05 BB)

Statistics on Mainland China

A critical review of mortality/incidence statistics in the PRC is being conducted to ascertain their usefulness for analytic purposes, and for planning of future studies of cancer-related diseases. Although the vital statistics system was introduced into China in the early 1900's, it was not until 1975 that a national survey collected cause of death data, supposedly for the entire country. No serious effort has been made to compile national statistics since. The published cancer volumes are more detailed and useful than the data available for non-cancer causes which are of limited value.

Mortality Trends by Nativity among U.S. Chinese

The eventual availability of 1980 U.S. Census data on Asians cross-tabulated by age-sex-nativity enabled us to pursue a trend analysis of mortality by nativity among U.S. Chinese around census years from 1960 to 1980. With the number of native-born Chinese aged 45 and over having increased about 2 1/2 times from 1960 to 1980, the new insights thus obtained would complement earlier study results on the Chinese in the U.S., Taiwan, Hong Kong, and Singapore. A preliminary review indicates that for almost every major non-cancer cause of death, the trend is downward for both nativity groups and sexes, with the exception of homicide. As for cancer the picture is mixed. There was a downward trend for such sites as nasopharynx, stomach, and uterus, but upward trend among native-born females for colon, pancreas, and breast.

Mortality Trends in Taiwan

A detailed time trend analysis of mortality by cause for Taiwan in the past four decades is being prepared, with emphasis on its comparability to that of U.S. Chinese.

Migrants to Taiwan from Fujian Province

Analysis of mortality data for the Taiwan population (originating in Fujian province on Mainland China) is approaching the final stage. The site-specific transitional experience is quite similar to earlier findings of the Chinese who migrated to Hong Kong and this country from Guangdong province (JAPH, March 84).

Asian Resource Data

A statistical file of age-specific and age-adjusted incidence and mortality rates for cancer/non-cancer causes since 1960 is being established, covering the Chinese, Japanese, and Filipinos in the U.S. and "home" countries. With continual updating, these figures provide background information on the health status of the Oriental populations in matters of hypothesis formulation and program planning.

Future Plans

Disease Patterns of Migrant Chinese and Japanese--Geographic, Generational, Temporal

A comprehensive analysis of disease transition by cause (cancer and non-cancer) will be initiated with emphasis on potential applications to the Division's control and prevention programs.

1. With the increasing number of U.S.-born Chinese in recent years, cancer risk ascertainment will be extended to making use of nativity information in SEER data for the first time; the study results would provide deeper insights into the site-specific status of U.S. Chinese.

2. A study of mortality/incidence patterns of Japanese populations by major causes at geographic, generational, and temporal levels, with special reference to planning for cancer prevention and control programs of the Division.

3. Current SEER coding practices only allow separate identification of four major Asian/Pacific Island populations. An initial step towards future studies of Koreans, Vietnamese, and Asian Indians, requires collaboration with the Demographic Analysis Section in efforts to obtain more detailed ethnic codes in SEER registries.

Development of Cancer Control Epidemiologic Methods (Z01 CN 00122-04 BB)

The purpose of this project is to develop the methodology of cancer control epidemiology, with emphasis on its conceptual foundations in biological, epidemiological, statistical, and ethical theory. Research areas include: concepts of cause and prevention, the logic of epidemiologic inference, the structure of causal and preventive models, the relationship of biological models of carcinogenesis to causal and preventive models and to models of interactions, the analysis of epidemiologic reasoning, ethics of cancer control epidemiology, and the design and analysis of cancer control research studies. Specific examples of work underway in this project include:

Studies in Causal and Preventive Inference

Criteria for causal and preventive inference have been improved. Traditional criteria fall into two categories: those dependent upon the specific form of the hypothesis and those independent of the form of the hypothesis. Two general criteria replace all existing criteria and have the added advantage of being equally applicable to causal and preventive inference. These are: predictability and testability. These criteria are currently being applied to these hypotheses: dietary alcohol causes breast cancer and dietary fiber prevents colon cancer.

Other research underway includes: predicting magnitudes of effect from the sufficient component causes model and a critical examination of the role that the magnitude of association plays in making causal and preventive inferences.

Studies in Causal and Preventive Interactions

An examination of the links between biological, statistical, and public health interaction reveals that although simple statistical models of interaction are testable, limiting attention to additive and multiplicative models alone is inadequate unless they can be tied to more explanatory biological theories. In addition, the additive model of causal interaction and the multiplicative model for preventive interaction should not be used as thresholds for recommending public health actions. Instead, these decisions should be based upon the balance between the risks and benefits of removing one interacting factor or the other. Such decisions are generally independent of considerations regarding whether some threshold level for combined risk has been exceeded.

In a separate effort, a new causal theory (epigenesis theory) has been developed as an elaboration of the sufficient component causes model and is being applied to the evaluation of causal and preventive interactions.

The Analysis of Epidemiologic Reasoning

A logical method, based upon critical deductive reasoning and therefore suitable for the mega-analysis of epidemiologic reasoning, has been developed and is being applied to: the use of case-control methods for screening, the use of negative results in causal and preventive inference, the debate regarding the use of either p-values, confidence limits, or p-value functions as the best way to report epidemiologic studies, the role of complexity in causal inference, and the links between scientific, technologic, and ethical reasoning when the epidemiologist is faced with the question: "does exposure to alcohol cause breast cancer?"

The Ethics of Prevention

Current literature suggests that epidemiologists should either get directly involved in preventive policy decisions at both the population and individual level, or provide scientific information only without recommendation as to its application. In this effort, the ethics of each choice are described, in order to provide the theoretical justification for personal choices on the part of cancer control epidemiologists.

Phase IV Studies of Cancer Control

Criteria for considering whether a cancer control study qualifies as a Phase IV, defined population study are described and the use of the randomized trial paradigm for the purpose of studies in defined populations is criticized.

CLINICAL AND DIAGNOSTIC TRIALS SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Engages in independent and cooperative research on statistical methodology for design of controlled clinical trials of cancer prevention and treatment and for field testing of diagnostic techniques;

- provides full statistical support in selected trials, including development of the detailed study plan, supervision of data collection, processing, and editing, and analysis of the data as well as preparation of scientific papers;

- develops statistical techniques for analyzing trial results, for identifying prognostic factors and diagnostic determinants, and for analyzing observational data;

- consults and collaborates extensively with other researchers requiring expertise in these and related areas."

Statistical Methodology Research (Z01 CN 00116-05 BB)

Adjusting for Correlated Variables in Regression

Investigations using theoretical derivations and computer simulations are being performed to investigate proposed methods for adjusting on highly correlated variables in a regression analysis, such as often occurs in the analysis of dietary data in studies of cancer risk factors. This investigation focuses on problems in using residuals of one dietary variable regressed on another, and also studies the effect of categorization into percentiles.

Analysis of Dietary Data

This project focuses on methodological difficulties which confront any analysis of the relationship between daily intake of several dietary components (total caloric intake, fat, protein, carbohydrates and fiber intake) and breast cancer incidence in the first National Health and Nutrition Examination Survey (NHANES I) follow-up study cohort. Three difficulties are being addressed: (1) Separating the specific effect of each nutrient in the presence of high collinearity between some of them; (2) The large intraindividual variation in the daily intake of all nutrients in the employed "24 hour recall" method; (3) The possible sensitivity of the estimated "effects" and their standard errors to the model specification.

In work to date the diet - breast cancer relationship has been examined through alternative logistic models exhibiting different model specifications and different degree of collinearity between the dietary exposure variables. This work has led to: (1) A collinearity diagnostic procedure for a logistic regression analysis which provides guidelines for distinguishing between changes in nutritional relative risk estimates due to confounding effects and instability in the relative risk estimates due primarily to multicollinearity. (2) Relative risk estimates for breast cancer associated with several alternative specifications of nutritional exposure and more "robust" relative risk estimates derived using the sample design weights. (3) Results which suggests that higher daily intake of protein may have a different role in younger and older women. (4) Differences in diet - breast cancer relationship between the two components of the NHANES I nutritional assessment: the 24 hour recall questionnaire and a limited food frequency questionnaire.

Work is ongoing to examine the sensitivity of some bias-corrected relative risk estimates and their standard errors to measurement errors in the 24 hour recall estimates of the dietary intake. This project is studying the sensitivity of the risk estimates to: different magnitude of the measurement errors; different pattern of correlation between measurement errors for various nutrients; and different model specifications which exhibit different degree of collinearity between the nutritional exposure variables. Appropriate software is being developed for these analyses.

Doubly Sampled Survival Data with Informative Censoring

In most survival studies subjects are followed until failure or censoring and no postcensoring failure data are available. Furthermore, censoring is almost always assumed to be noninformative. However censoring may be informative in many real life situations, for example, when patients drop out of a study for reasons related to their health. In such a case the investigator may take a subsample of the studied population and follow subjects who have been censored to their postcensoring failure time. Such data is called double sample survival data. This project, in collaboration with the Screening Section, has shown how the double sample data can be used to derive maximum likelihood estimates for parameters of a logistic regression model for the failure rates, when time is considered discrete and for a set of categorical covariates. Also, a generalized log rank test has been formulated for the hypothesis that censoring has no prognostic effect on failure time.

This methodology is being applied to a postoperative wound infection study carried out in Israel in 1982-1983. In particular the risk of wound infection following a hernia operation is being examined, using some 1987 hernia patients from 11 hospitals who were followed until discharge, or for 30 days if discharge occurred later, and a subsample of 194 patients who were followed up also for possible post-discharge infection. Following this, the goal is to extend the basic approach to continuous failure time and any set of covariates.

Assessing Power Gains from Matching on Predictor Variables in Intervention Studies

In intervention studies, particularly when groups such as communities are the units of randomization, matching may be done to increase the power for detecting a treatment effect. At the time of initiation of the study, it may be possible to estimate the gain in power which will result from the matching, by using a variable which acts as a surrogate for the outcome measure. For example, in a smoking cessation study, past quit rate is a possible surrogate for future quit rate. Using data from the baseline survey of the Community Intervention Trial for Smoking Cessation, methods were investigated for assessing the power achieved by matching, and for evaluating the effect of using the surrogate variable itself either in the original matching or for balancing the randomization.

Sample Size Computer Program

Development has continued on a program to compute power and sample size for a variety of experimental design situations. The program operates interactively on the NIH DEC-10 computer system. The program is user-friendly and prompts for answers to design questions. Optional user instructions provide a description of program capabilities as well as citing literature from which equations used in the calculations were adapted. A frequently used part of this program are power calculations associated with an accrual trial.

Interactive Data Analysis Programs

The Section has previously developed and continues to maintain and improve a group of interactive computer programs for efficient analysis of medical data, particularly those dealing with risk factors and prognostic factors using sophisticated multiple regression techniques and survival analysis. These programs have proven useful not only for many projects within the Biometry Branch but also elsewhere in the Division, as well as by other investigators both within the NIH and at outside institutions. During the past year, there was particular interest in the program for analyzing time-dependent covariates, and special versions of this program were produced to handle larger datasets.

Consultation on Clinical Trials and Other Studies (Z01 CN 00119-05 BB)

Community Intervention Trial for Smoking Cessation

Extensive consultation has been provided to the staff of the Smoking, Tobacco, and Cancer Program concerning design issues which have arisen in the planning of a large-scale community-based study intended to promote smoking cessation among heavy smokers. Staff of the Biometry Branch have devised the basic design for the study, eleven matched pairs of communities with one member of each pair chosen at random for intervention and the other serving as a control. The study was designed to detect a 10% difference in the smoking quit rate between the intervention and control communities.

Members of the Biometry Branch had convinced the Steering Committee at its first meeting that it was most important that the baseline survey be completed before any active community involvement in any of the twenty-two communities, and particularly before randomization. Biometry Branch staff have been actively involved in all meetings of the Steering Committee and have assisted in the questionnaire design, preparation of the OMB package for survey approval, and analysis of community demographics to assess comparability of matched communities. The baseline survey was completed in May of 1988. Cohorts of heavy, light-to-moderate, and recent ex-smokers were identified for follow-up. Analysis of demographics showed comparability of community pairs as previously shown by U.S. Census data. Members of the Biometry Branch designed and implemented the method for random assignment of communities. Randomization occurred at the May meeting of the Steering Committee, and community involvement in each of the eleven intervention communities was begun. Surveys to track and evaluate the effectiveness of the various intervention channels were designed, and a contractor was selected to begin collecting these data in the fall of 1988.

Brain Tumor Clinical Trials

The Section provides full support for the Brain Tumor Cooperative Group, a multicenter group of neurosurgeons, neuro-oncologists, radiotherapists, neuroradiologists and neuropathologists conducting randomized trials for patients with primary brain tumors (with emphasis on malignant gliomas). The Group has designed and has begun accruing patients to a new phase III trial, BTCG 87-01, to study interstitial radiation (seed implants) as an addition to the customary external beam radiation and chemotherapy. The Group has also now implemented a new randomized study for low-grade glioma patients, BTCG 87-30. This study compares immediate versus delayed radiotherapy; for the delayed arm, radiotherapy is only given at the time of documented tumor progression. Planning has proceeded to do this trial as an intergroup study with two other cooperative groups, RTOG and SWOG. In addition, there are currently two older trials accruing patients: BTCG 84-20 A is a randomized phase II comparison of intra-arterial cisplatin versus intravenous PCNU for primary brain tumors; the Group is currently evaluating interferon in a non-randomized phase II study (BTCG 84-20 B).

Follow-up has continued for previous BTCG studies. Analyses using updated follow-up data were completed for studies 80-01 and 77-02. BTCG 80-01 is a phase III trial which compared three different chemotherapy approaches and also compared 6000 rad whole brain irradiation versus 4300 rad whole brain plus 1700 coned down to the tumor volume. The conclusions of the study were that giving part of the radiotherapy by coned-down port was as effective as full whole brain irradiation, but that giving multiple drug chemotherapy as outlined in the protocol conferred no significant survival advantage over BCNU alone. BTCG 77-02 is an earlier phase III trial which compared four arms. The conclusion of the completed analysis was that neither the addition of the radiosensitizer Misonidazole nor hyperfractionated radiotherapy offered any advantage over conventional radiotherapy plus either BCNU or Streptozotocin for treatment of malignant glioma. The Group continues to investigate improved approaches to the multimodality therapy of brain tumors.

Multiple Regression Analyses of Risk Factors for Breast Cancer

In collaboration with the Cancer Prevention Studies Branch, analyses of data from the Framingham Heart Study Cohort have investigated alcohol consumption as a risk factor for breast cancer, while adjusting for other known risk factors. Analyses were carried out using both single (baseline) alcohol measures and repeated alcohol measures (with alcohol intake and menopause status being modeled as time-dependent covariates). The conclusion is that alcohol consumption was not associated with an increased risk of breast cancer in this cohort.

In collaboration with the Epidemiology and Biostatistics Program, DCE, analysis of data from the Breast Cancer Detection Demonstration Project (BCDDP) and from the Cancer and Steroid Hormone Study (CASH) has continued. The goal is to investigate regression models of risk factors which could be used to advise women on their breast cancer risk. Recent work has focused on interactions between risk factors in the model.

Finally, in collaboration with the Cancer Prevention Studies Branch, other data from the BCDDP, which include additional prospective follow-up, are being analyzed, looking at a number of variables, including various aspects of benign breast disease, as risk factors for subsequent development of cancer. Analyses of 34,597 participants (529 who developed breast cancer) via the Cox proportional hazards model identified age at first live birth, age at first use of a birth control pill, age at exogenous hormone use, high family income, tallness and religious preference as being associated with an increased risk of developing breast cancer in these normal women and women with benign breast disease. In addition, at the request of researchers from Vanderbilt University, a subset of this database was created for a matched case-control study.

Design and Analysis of Pharmacokinetic Studies of Selenium (Z01 CN 00107-06 BB)

Selenium is a possible cancer preventive agent and is being considered for use in intervention trials. A study (Z01 CN 00107-06 BB) in collaboration with the Cancer Prevention Studies Branch is in progress which will provide information on the pharmacokinetics of selenium in its prototype forms--sodium selenite (inorganic form) and selenomethionine (organic form). This information is necessary for the determination of time and manner of administration. In the study, 32 subjects received a single oral tracer dose of selenite or selenomethionine on 2 occasions, 90 days apart, once fasting and once non-fasting. A kinetic model for selenite has been developed. This model includes absorption distributed along the GI tract, transport through four plasma components, a subsystem consisting of the liver and pancreas, and a slowly turning over tissue pool. Mean residence times for the various components and subsystems were calculated; these were longest for the peripheral tissues, ranging from 115-286 days. Using this model, we predict that after 90 days 40% of the dose would be retained in the tissues.

An objective of the study was the comparison of pharmacokinetic parameters in fasting and non-fasting subjects. Analysis of selenite tracer data suggests that fasting status modulates the effects of the first plasma component. While absorption is similar in both fasting status, there appears to be a greater first pass effect in non-fasters, probably in response to eating. Such information is important in deciding on an optimal dosing regimen. Results have been presented at a national and at an international meeting.

Another aspect of the project is an analysis of variations in total selenium levels in the plasma, urine and feces both within and between individuals. This information is important in deciding what measures can be used to determine selenium status. In addition, statistical support is being provided on an analysis of the relationship of dietary intake of selenium and the levels in the blood, hair and nails in a sample of individuals living in South Dakota, an area where selenium levels in the soil are high.

Population Consumption of "Protective" or "Harmful" Foods

In order to carry out prevention programs aimed at reducing cancer incidence through dietary modifications, it is necessary for policy makers to have a clear picture of the American diet. A study examining the consumption of foods and food groups thought to be harmful or protective with respect to the development of cancer was completed, and materials prepared for dissemination to the press. The study was done in collaboration with the Surveillance and Operations Research Branch, and press materials developed working with the Office of Cancer Communications. The choice of food groups was based on dietary guidelines issued by the National Research Council (interim guidelines in Diet, Nutrition and Cancer) and the American Cancer Society. The study used twenty-four hour dietary recall data, from the Second National Health and Nutrition Examination Survey. The analysis was stratified by sex, race, age group, poverty index, and region. The analysis showed that, on the recall day, 41% of the adult population did not eat even a single serving of fruit (including fruit juices), and 17% consumed no vegetables. Consumption was more limited for fruits and vegetables high in vitamin A (21%) and vitamin C (28%), and for high fiber breads and cereals (16%).

Following publication and a press release, the study received widespread coverage in radio interviews and in newspapers, magazines, and scientific and professional publications. Such coverage may increase public awareness of the dietary cancer guidelines as well as the need for increased consumption of fruits, vegetables, and whole grains.

A related study, also in collaboration with the Surveillance and Operations Research Branch, is underway. Using the same database, the proportions of the population meeting the USDA Guidelines concerning fruits and vegetables (2 or more servings of fruit and 3 or more servings of vegetables) are being examined by race, sex, and broad age groups. In addition, the proportions consuming fruits and vegetables are being examined by numbers of servings, and, for vegetables, the composition of the servings (potatoes, garden vegetables, dried peas and beans, salad) is being investigated.

Intake Patterns of Dietary Fats

Because of hypotheses and recommendations concerning the relationship of diet to cancer and heart disease, a study was undertaken investigating patterns of intake of the following nutrients and dietary factors: energy (calories), total fat, saturated fat, oleic acid, linoleic acid, dietary cholesterol, P/S ratio, and percent of calories from fat. This study, done in collaboration with the Surveillance & Operations Research Branch, has now been completed. Twenty-four hour dietary recall data from the NHANES II survey were used. Dietary intake was expressed both in absolute terms and per unit of body weight, and presented by race, sex, and age. For most age and sex categories, blacks were found to have a lower intake of energy and fats, a difference which appears to be independent of poverty status. However, blacks had a consistently higher intake of dietary cholesterol. P/S ratio was higher in females than in males, but all age-sex groups were substantially below recommended levels. Percent of calories from total and saturated fat were similar in most age-sex groups. Some possible explanations of the observed patterns were explored.

Study of Food Purchasing Behavior and Consumer Nutrition Education

The Clinical and Diagnostic Trials Section is providing statistical support to a project undertaken jointly by the Surveillance and Operations Research Branch of the NCI and Giant Food to test the effectiveness of several supermarket intervention strategies for changing food purchase behavior. The goal is to increase the purchase (and the consumption) of foods high in fiber, thus reducing cancer risk. Using baseline year data, methods are being developed to examine both changes in the proportions of recommended versus non-recommended foods purchased in a given food category (e.g. high-fiber breads versus their lower-fiber counterparts) and changes in the overall purchase of whole categories (e.g. vegetables). A model is being developed which takes into account such variables as price and seasonality.

Diet and Prevention of Gastric Cancer

Although gastric cancer has been declining, it remains a significant problem worldwide. Many dietary risk factors have been implicated for this cancer, particularly for the intestinal type, and it is therefore a candidate for intervention to prevent the disease. In addition, precursor lesions (e.g., chronic atrophic gastritis) are of interest, and markers for such conditions (e.g., serum pepsinogen) may be relevant to the design of studies.

The Clinical & Diagnostic Trials Section in conjunction with the Diet and Cancer Branch organized a workshop held at NIH (with international participation) to address questions concerning what specific data justify an intervention trial and what additional data are needed to make a trial feasible; which intermediate endpoints (e.g., serologic, histologic) should be used in an intervention trial; what populations should be considered for studies; and which interventions are most promising (e.g., micronutrients, additions to diet of fruits & vegetables, decreasing intake of purported harmful substances). Also, issues in the design of prevention trials for this disease were presented in London at a Symposium on Gastric Carcinogenesis.

The National Death Index

The National Death Index (NDI) offers an efficient method of ascertaining mortality and subsequently obtaining cause of death for the large numbers of persons involved in studies conducted or funded by the NCI. Efforts to acquaint cancer researchers with the NDI and its uses in treatment and prevention trials and in epidemiologic and occupational studies began in 1984. A Working Group, appointed in September 1985 by the Director of the NCI, has developed an NCI-wide policy concerning use of the NDI. Advice and information were sought from staff within the NCI, the NIH, and the NCHS on legal and administrative issues related to privacy, confidentiality, and policy implementation. The Group has explored the different requirements for setting policy in intramural research, contracts, grants, and cooperative agreements. A package giving a draft policy and a discussion of problems associated with implementation has been prepared and sent to the Director, NCI.

SCREENING SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Plans, conducts and analyzes independent and cooperative research studies in screening for the early detection of cancer;
- conducts methodologic research in statistics, probability and epidemiology with particular emphasis on techniques appropriate to the design, analysis, and modeling of randomized and observational studies in cancer screening and related areas;
- engages in independent and cooperative research to determine cancer natural history and risk characteristics of populations for application to the design and interpretation of early detection and related studies;
- maintains liaison with other agencies, organizations and professional societies concerned with cancer screening and related methodology in order to coordinate and optimize activities."

Studies in Cancer Screening (Z01 CN 00106-06 BB)

Data from several cancer screening studies are being collected and analyzed to gain a better understanding of the impact and consequences of such screening in various population settings. Staff are involved in design, monitoring, and data analysis aspects of these studies. The results can be used by the NCI in establishing cancer control policy. These data bases also provide an opportunity for the development and testing of new techniques for data analysis. The studies fall into two main categories: randomized trials and observational studies.

Randomized Trials

Three large-scale randomized trials have been conducted by the NCI to evaluate screening for breast, lung, and colorectal cancer. Staff participate in the analysis of completed studies and conduct of ongoing studies. The data base from the HIP breast cancer screening trial was used to address several scientific and modeling issues. This study demonstrated a 25 percent reduction in breast cancer mortality after 10 years as a result of screening with physical examination and mammography, and has served as the basis for NCI policy and studies in other countries. Analysis focused on the magnitude and duration of the benefit, age-specific effectiveness, and application to model development and validation. Data from the lung cancer screening trials conducted at Johns Hopkins University, Memorial Sloan Kettering Hospital, and the Mayo Clinic were edited and analyzed. Initial investigations included assessment of incidence, staging, survival, and mortality information. The colorectal cancer screening trial at the University of Minnesota is currently in progress to evaluate testing for occult blood in the stool as an early detection maneuver for colorectal cancer. Staff participate in scientific consultation and ongoing data monitoring for this study.

Observational Studies

In collaboration with researchers from the Centocor Company, the value of using the CA125 assay as a component in the early detection of ovarian malignancy is being studied. At this point serial evaluation of serum CA125 levels over a two year period for women at least 39 years of age has been completed. The results indicate the CA125 assay can be valuable for identifying women in a normal population that are at high risk of ovarian malignancy. Screening for bladder cancer in a high risk occupational cohort is also under investigation. In a collaborative effort, data from the bladder cancer screening program at the DuPont Company are being analyzed to relate disease characteristics and outcome to urine cytology and blood tests, smoking history, and exposure to benzidine and beta-naphthylamine. The tests are being evaluated as indicators of exposure, predictors of disease, and for their possible impact on disease outcome through early detection.

Research in Cancer Screening and Statistical Methodology (Z01 CN 00105-06 BB)

The focus of this project is the development and refinement of statistical procedures for the design and analysis of cancer screening and related studies. Problems under investigation include an examination of analysis methods and endpoints for screening studies, assessment of case-control studies for screening evaluation, development of cancer screening models, and derivation of novel approaches to the analysis of categorical data. Each of these problem areas is common to screening and prevention studies in which the Division participates, but the methods for screening studies must address the special lead time and length biases inherent in screening programs.

Case-Control Studies

In recent years, case-control methodology has been suggested for evaluating screening programs and a few studies using such methods have been carried out for cervical, breast, lung, and stomach cancer screening. At issue are the accuracy and applicability of this design for the evaluation of screening programs. Initial research to examine case-control studies within randomized trials of screening has been completed. Estimates of the screening effect based on case-control methodology were compared to those based on the randomized trial design. Alternative definitions of cases, controls, and exposure have been assessed, and the impact of various matching variables analyzed. Data from the HIP breast cancer screening trial has been used in this analysis. The results indicate the case-control methodology can be valuable in assessing the benefits of screening programs. However, one must exercise great care because with inappropriate matching variables misleading results can be obtained.

Stage-Shift Screening Model

A stage-shift cancer screening model has been developed. The model provides a framework so that results of a randomized controlled trial of cancer screening can be studied in greater depth. It uses the number of cancers diagnosed by stage for the screened and control groups to estimate the number of cancers shifted from their usual stage in the absence of screening to a lower stage. Mortality and survival data are then used to estimate which stage shifts are beneficial in reducing mortality or extending survival. Application of the model to the HIP breast cancer screening study indicated that most of the detected breast cancers are usual stage I and II breast cancers that have a poor prognosis, and that almost all of the mortality reduction due to screening is a result of these cancers being detected and treated earlier than usual.

Choosing Sample Sizes To Maximize Expected Health Benefits Subject to a Constraint on Total Trial Costs

A method has been developed for choosing sample sizes for randomized controlled trials which maximizes expected health benefits (measured in expected discounted life years gained) subject to the decision maker's budget constraint. In comparison with similar approaches, this method introduces richer and more realistic models for the following quantities: costs and benefits during and after the trial, rates of adopting interventions after a positive recommendation, the distribution of data collected in the trial, and the decision to make a positive recommendation based on the results of the trial. Although the methodology is applicable to any type of trial, the emphasis is on prevention trials. Calculations involve Monte Carlo methods. A hypothetical choice of sample size for two screening trials illustrates the method.

Periodic Screening Evaluation: A Method to Evaluate Long-Term Screening Using Data from Short-term Screening With No Controls

Screening for the early detection and treatment of disease has the potential to reduce mortality from disease among large numbers of individuals. Recommendations for screening often take the form of periodic screening: screening at regular intervals starting at some age. Sometimes a major source of data for making recommendations about periodic screening comes from short-term screening studies with no control group (consisting of individuals not offered screening or randomized to no screening). A newly developed approach, called PSE, uses such data to estimate the change in rates of death from disease associated with various ages to begin periodic screening. PSE represents a substantial improvement over other methods for analyzing data from a screening study which has no control group. Unlike other methods, PSE evaluates various ages to begin periodic screening, PSE does not require independent sojourn times or parametric (except multinomial) distributions for sojourn times, and PSE yields closed-form estimates for special cases, which provide important insights into the identifiability of parameters. PSE was applied to data on individuals offered screening in the Health Insurance Plan of Greater New York (HIP) study. Estimates were obtained for the change in life years and probability of death from breast cancer due to starting periodic screening for breast cancer at various ages between 40 and 64. Data on individuals randomized to no offer of screening were used for validation.

Two-Process Models for Discrete-Time Serial Categorical Response

Sometimes a polychotomous response is generated for each subject under study at successive discrete intervals. Response type at each discrete time may be either a transient response or a cause-specific failure. Because the outcome of transient response is fundamentally different than the outcome of failure, a separate model is necessary for each: one model describes the process for transitions to transient response states and another one describes the process for transitions to absorbing failure states. The likelihood for each model is separately maximized using existing software for iterative proportional fitting.

Regression Models for Doubly Sampled Categorical Data With Nonignorable Sampling Mechanisms and Partial Validation

In many studies it is easier to obtain a surrogate measure of outcome (surrogate response) than a true measure of outcome (true response). If an investigator is interested in the relation between covariates and true response, he may collect two samples of data: the investigation sample, which contains data on covariates and surrogate response, and the validation sample, which contains data on true response, surrogate response, and perhaps covariates. Because the surrogate response is easier to obtain than the true response, the investigation sample is typically much larger than the validation sample. These two samples are called doubly sampled data. The methodology focuses on the regression analysis of doubly sampled categorical data.

Previous methods for the regression analysis of doubly sampled categorical data have required that the two samples be random samples from a single population. This method does not require such a restrictive assumption. Also, previous methods have paid little attention to the case when the validation sample excludes covariates (which we call partial validation, as opposed to full validation which includes covariates). Partial validation is most likely to arise when the ascertainment of covariates is difficult or expensive. For doubly sampled data with partial validation, closed form maximum likelihood estimates have been derived including a unique closed form estimate for a model in which unique estimates had not been thought to exist. The methodology may be applicable to the analysis of data on diet and cancer.

Endpoints for Screening Evaluation

The population mortality rate is the only known unbiased endpoint for assessing the impact of cancer screening. Determination of this rate usually requires long term follow-up data. Results of screening studies could be obtained sooner and at less cost if the screening effect could be measured accurately using a short term endpoint which was a valid proxy or predictor of mortality. Suggested early endpoints include case survival and shift in stage distribution, but these are known to be influenced by lead time and length biases. A more promising outcome variable is the incidence rate of advanced stage disease. This research involves a comparison of this rate and other measures with mortality. Data from the HIP breast cancer screening trial and the NCI sponsored lung cancer screening trials are being used to address these comparisons.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00143-04 CPSB

PERIOD COVERED

October 1, 1987 - September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Continued Follow-up of the Breast Cancer Detection and Demonstration Project

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI's:	P.R. Taylor	Branch Chief	CPSB, DCPC, NCI
	R.N. Hoover	Branch Chief	EEB, DCE, NCI
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COOPERATING UNITS *(if any)*

Environmental Epidemiology Branch, DCE
Early Detection Branch, DCPC (C. Smart)
Biometry Branch, DCPC (D. Corle)

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The BCDDP screening program began in 1973 in 29 centers in 27 widely dispersed geographic areas of the United States. Initial screening was complete on over 280,000 women over a 2-year period. From the original 280,000 participants in the screening phase of the BCDDP, approximately 64,000 were selected for 5 years of long-term follow-up (LTF) beginning in 1978, to assess the biology and natural history of breast disease, and to test hypotheses relating to detection, etiology, and survival. Those selected for LTF included all breast cancer cases found during the screening phase, all benign breast cancer cases, all those recommended for biopsy, and a sample of "normals." The LTF database will facilitate the exploration of important questions regarding the etiology and natural history of breast cancer. The size of the subcohorts and breadth of data available on them make this population unique. The large number of cases of both breast cancer and benign breast disease with histologic information available should allow particularly useful analyses of several risk factors in relation to these conditions.

The first 5 years of LTF was completed in all centers in September 1986, and a further continued follow-up has begun.

This project is being conducted jointly by the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control and the Environmental Epidemiology Branch of the Division of Cancer Etiology.

PHS 6040 (Rev. 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00145 03 CPSB

PERIOD COVERED

October 1, 1987 - September 30, 1988

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders)

Linkage of Classical and DNA Markers to the Susceptibility Gene for Breast Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: C.L. Carter Staff Fellow CPSB, DCPC, NCI

COOPERATING UNITS (if any)

LAB/BRANCH

Cancer Prevention Studies Branch

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.25	0.25	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type Do not exceed the space provided)

The overall goal of this project is to further an understanding of the genetic, environmental, and cultural influences that are involved in the etiology of human breast cancer. The specific aim is to test for genetic linkage between a large array of discrete, polymorphic genetic markers and the gene(s) for breast cancer in family data. The ultimate goal is to localize a gene or genes that predispose women in high-risk families to breast cancer. A sample of women with a strong family history of breast cancer who participated in the Breast Cancer Detection Demonstration Project (BCDDP) will be contacted and pedigree, vital status, health history, and epidemiological data will be collected from them and their family members. Fifteen to twenty families whose pedigree structure appears to be the most informative for use in linkage analysis studies will be selected. Blood will be collected from family members and analyzed for the presence of a number of genetic markers, including blood group antigens, red blood cell enzymes, plasma proteins, and restriction fragment length polymorphisms (RFLPs). Marker data results will then be used to perform computer generated linkage analysis.

This project started in September 1986 and will continue for 3 years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00104-06 CPSB

PERIOD COVERED

October 1, 1987 - September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

NHANES I Epidemiologic Follow-up Survey: Chemoprevention/Nutrition Aspects

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	P.R. Taylor	Branch Chief	CPSB, DCPC, NCI
Others:	D. Albanes	Staff Fellow	CPSB, DCPC, NCI
	G. Block	Epidemiologist	SORB, DCPC, NCI
	C.L. Carter	Staff Fellow	CPSB, DCPC, NCI
	A. Schatzkin	Staff Fellow	CPSB, DCPC, NCI
	C.A. Swanson	Staff Fellow	CPSB, DCPC, NCI
	R. Ballard-Barbash	Staff Fellow	CPSB, DCPC, NCI
	M. Reichman	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS (if any)

This research developed as a collaborative effort by NCHS and various institutes at NIH: Biometry Branch, DCPC, NCI; NIA; NIMH; NIAAA; NHLBI; NINCDS; NIADDK; NIAID; National Center for Health Statistics

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of the NHANES (National Health and Nutrition Examination Survey) Initial Epidemiologic Follow-up Survey was to conduct a longitudinal study of 14,407 adults originally surveyed in 1971-75, to investigate subsequent health and mortality outcomes. Respondents have been traced and re-examined. Additional information was obtained from hospital records, the National Death Index, and death certificates. The NHANES Initial Follow-up Survey was completed in 1984.

The purpose of this intramural project is to examine the relationship of chemopreventive and nutritional factors as well as constitutional factors to cancer in this representive population. This study provides an opportunity to examine these factors and potentially confounding or modifying factors in a prospective fashion, and to examine the effectiveness of dietary agents which are currently of great interest for cancer prevention. The relationship of baseline vitamin use, biochemical or nutritional measures, and subsequent health status will be examined. In addition, descriptive data and trends in potential risk factors or prospective factors over time will be examined. A continued follow-up of the elderly (those over 75 years of age) was conducted in 1985-86, while the entire cohort was followed up in 1986-87.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00101 06 CPSB

PERIOD COVERED

October 1, 1987 - September 30, 1988

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.)

Human Studies of Diet and Nutrition

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	P.R. Taylor	Branch Chief	CPSB, DCPC, NCI
Others:	A. Schatzkin	Staff Fellow	CPSB, DCPC, NCI
	C.A. Swanson	Staff Fellow	CPSB, DCPC, NCI
	E. Lanza	Sr. Chemist	DCB, DCPC, NCI
	B.H. Patterson	Math. Statistician	BB, DCPC, NCI
	B.K. Edwards	Biostatistician	SORB, DCPC, NCI
	M. Reichman	Staff Fellow	CPSB, DCPC, NCI
	R. Ballard-Barbash	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS (if any)

U.S. Department of Agriculture, Beltsville Human Nutrition Research Center; Surveillance and Operations Research Branch, Biometry Branch, and Diet and Cancer Branch, DCPC; Armed Forces Institute of Pathology (M. Micozzi)

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER
3.0	2.25	0.75

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type Do not exceed the space provided.)

The role of dietary factors in cancer prevention has been assessed in animal experiments, in human epidemiologic studies, and most recently, in prevention trials. For many of these agents, however, information is incomplete concerning their safety, toxicity, dose, form, bioavailability, pharmacokinetics, and mechanisms of action. To further define these parameters in humans, a cooperative research effort between the Beltsville Human Nutrition Research Center (BHNRC), U.S. Department of Agriculture, and the CPSB, DCPC, is being conducted. Initial efforts have focused on three nutrients which have shown the most promise for cancer prevention--selenium, fat, and beta-carotene.

A study of the kinetics of a single, oral dose of two forms of selenium in the fasting and non-fasting state was conducted in the first year. Current activities include evaluations of the safety/toxicity of selenium and form of ingestion among persons residing in seleniferous areas.

Studies examining the metabolic effects of changes in dietary fat and fiber have been conducted separately in premenopausal women, postmenopausal women, and men. These dietary changes are being related primarily to serum lipids, hormonal status, bile acid metabolism, and fecal mutagenicity.

Beta-carotene studies are examining the plasma carotenoid response to single and long-term ingestion of beta-carotene from either a capsule or from selected vegetables.

Studies of the effects of alcohol on hormonal status, of the kinetics of vitamin C, and of the influence of omega-3 fatty acids on prostaglandins are planned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00100 06 CPSB

PERIOD COVERED

October 1, 1987 - September 30, 1988

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.)

U.S. Finland Studies of Nutrition and Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	D. Albanes	Staff Fellow	CPSB, DCPC, NCI
Others:	P.R. Taylor	Branch Chief	CPSB, DCPC, NCI
	B.K. Edwards	Biostatistician	SORB, DCPC, NCI
	A.M. Hartman	Health Statistician	SORB, DCPC, NCI
	C.L. Carter	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS (if any)

National Public Health Institute, Helsinki, Finland
Surveillance and Operations Research Branch, DCPC

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.75	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The important relationship of diet and nutrition in the development of cancer has become well known through various research efforts. Laboratory studies have shown cancer inhibitory function for various natural and synthetic nutrients in various models, which have been corroborated by human epidemiologic studies of nutrient intake, tissue levels, and cancer incidence. Vitamin A, beta-carotene, and selenium have been strongly implicated for their cancer preventive potential, with sufficient evidence for these substances to warrant their use in prevention trials. In addition, the roles of other nutrients in cancer cause and prevention (e.g., dietary fats and fiber) require further investigation.

The objectives of this cooperative project with the government of Finland are: 1) to determine if either beta-carotene or alpha-tocopherol supplement is effective in preventing lung cancer in smokers; 2) to better assess the role of fats, selenium, and vitamins A, E, and C in breast cancer development; and 3) to evaluate the relation of intake of various nutrients to subsequent cancer. The project includes three studies. The first is a 5-year, randomized, double-blind, placebo-controlled, 2x2 factorial prevention trial of daily beta-carotene (10 mg daily) and alpha-tocopherol (50 mg daily) among smokers at high risk for lung cancer. The difference in lung cancer incidence between intervention groups will be determined. The second is a breast cancer case-control study of fats, total calories, selenium, and vitamins A, E, and C. The role of various anthropometric measurements as well as genetic markers for breast cancer will be explored. The third project will be a comparison of nutrient intakes in cases and reference subjects identified from an existing large cohort with prediagnostic baseline dietary histories. Associations between various dietary components and several cancers will be assessed. Several pilot studies have been completed to date, and the prevention trial and breast cancer study are underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00103 06 CPSB

PERIOD COVERED

October 1, 1987 - September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Use of Isotretinoin in Prevention of Basal Cell Carcinoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.A. Tangrea	Deputy Branch Chief	CPSB, DCPC, NCI
Others:	P.R. Taylor	Branch Chief	CPSB, DCPC, NCI
	B.K. Edwards	Biostatistician	SORB, DCPC, NCI
	A.M. Hartman	Health Statistician	SORB, DCPC, NCI
	G. Peck	Senior Investigator	DB, DCT, NCI

COOPERATING UNITS *(if any)* Walter Reed Army Med. Ctr; Fitzsimons Army Med. Ctr; Brooke Army Med. Ctr; Eisenhower Army Med. Ctr; Portsmouth Naval Med. Ctr; Northwestern U.; U. of Arkansas; Roswell Park Med. Inst; Dermatology Br., NCI; Radiology Dept., Clinical Ctr; Surveillance & Op. Br., DCPC; Cancer Prev. Studies Br., DCPC

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0.00

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The study is a 5-year, randomized, double-blind clinical trial designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinoma in a high-risk population, and to examine possible side effects associated with long-term administration of low doses of isotretinoin. The recruitment phase of the study has been completed and 981 subjects have been entered over 36 months at 8 participating clinical centers located around the country. At each center, subjects have been randomly allocated to intervention (10 mg/day) or control (placebo) groups.

The rationale for this study includes the following. Laboratory experiments have shown that retinoids administered to animals can prevent chemical carcinogenesis. In the experimental animals, retinoids were effective even if administered after exposure to the carcinogen, and therefore the prophylactic effect of the retinoids is believed to be in the postinitiation phase, i.e., during the promotion phase of carcinogenesis. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinomas for 4 years in patients at higher risk of developing new tumors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00112 05 CPSB

PERIOD COVERED
October 1, 1987 - September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Nutrition Intervention Studies of Esophageal Cancer in Linxian, China

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PIs:	P.R. Taylor	Branch Chief	CPSB, DCPC, NCI
	W. Blot	Branch Chief	BB, DCE, NCI
Others:	J.A. Tangrea	Deputy Branch Chief	CPSB, DCPC, NCI
	A. Ershow	Staff Fellow	BB, DCE, NCI
	S. Dawsey	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Cancer Institute, Chinese Academy of Medical Sciences, Beijing, The People's Republic of China; Biostatistics Branch, DCE, NCI

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS 2.0	PROFESSIONAL 2.0	OTHER

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to conduct two intervention trials using multiple vitamin-mineral supplements to evaluate the relationship between such supplements and esophageal cancer incidence and mortality. One trial is being conducted in patients diagnosed with esophageal dysplasia (n = 3400) and the other in the general population in a high-risk region (n = 30,000). The effect of these supplements on regression/progression of esophageal dysplasia and total cancer incidence, total cancer mortality, and total mortality will be evaluated. These two studies are being conducted in Linxian (Henan Province) in the People's Republic of China (PRC). Linxian, a rural country with population 800,000, was selected because it has the highest rate of esophageal cancer in the world (>100/100,000) and because there is suspicion that the population's chronic deficiences of multiple nutrients may be etiologically involved.

This study is being conducted jointly by the Biostatistics Branch of the Division of Cancer Etiology and the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control at the NCI in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00142-04 BB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cancer Control Objectives and Cancer Mortality Projections

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. L. Levin, M.D.	Senior Investigator	BB, DCPC, NCI
Others:	L. G. Kessler, Sc.D.	Chief	SORB, DCPC, NCI
	J. Horm, M.S.	Statistician	SORB, DCPC, NCI
	M. H. Gail, M.D.,Ph.D.	Statistician	BB, DCE, NCI
	A. Potosky	Operations Res. Analyst	SORB, DCPC, NCI
	L. Ries, M.S.	Statistician	SORB, DCPC, NCI

COOPERATING UNITS *(if any)*

Surveillance and Operations Research Branch, DCPC
Biostatistics Branch, DCE

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Office of the Chief

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.2	1.1	0.1

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Projecting cancer incidence and mortality rates, and relating those projections to the attainment of national cancer control objectives are the goals of this intramural research project. The project includes development and continued refinement of a computer model which projects cancer incidence and mortality, meshing together data from a variety of sources, and adapting quantitative cancer control objectives to fit the modeling framework.

The NCI staff has developed and written a large interactive Fortran program for the NIH DEC-10 computer used to project cancer figures from 1980 through the year 2020. The model incorporates different models for survival from cancer, includes data for a number of cancer sites, the ability to examine temporal trends in underlying cancer incidence and mortality from other causes, adjustment of rates to different populations, and production of annual projections of cancer incidence and mortality. The crux of the model is the flexibility to analyze the effect of cancer prevention, screening, and treatment activities (in any combination) on cancer mortality.

Work in the current year has involved analysis of trials in breast cancer, projections on a state level, and updating of the basic underlying database used by the program.

PHS 6040 (Rev 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00121-04 BB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders)*
Research in Biostatistical Methodology and Mathematical Modeling

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

PI:	C. C. Brown	Chief	BMCCES, BB, DCPC, NCI
Others:	R. R. Connelly	Statistician	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided)*

The purpose of this project is development of biostatistical methods and mathematical models appropriate for the analysis of epidemiologic and experimental studies related to cancer control and prevention. Many of the statistical problems being studied under this project are derived from the consultation activities of the Section.

Activities during the past year have been directed toward developing a method to reduce the bias inherent in the Robertson-Boyle solution to the nonidentifiability problem in age-period-cohort Poisson regression analysis; development of a GLIM regression method to allow unbiased estimation of the treatment effect in a randomized trial involving covariates measured with error; extension of the simple Goldie-Coldman model of tumor cell resistance to chemotherapy to include immunostimulation and time-varying birth, death, and cellular mutation; development of a computer program to statistically analyze unbalanced repeated-measures studies.

This project also includes research on the development and use of mathematical models of carcinogenesis to analyze cancer studies and to predict the results of intervention strategies; the Armitage-Doll model is being used to study the effect of time patterns of carcinogenic exposure on inferences regarding their joint action; the Moolgavkar-Knudson two-stage model is being used to quantify the hypothesized effects of a woman's first full-term pregnancy upon her future breast cancer risk.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00115-05 BB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders)*
Descriptive Cancer Epidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name. title. laboratory. and institute affiliation)*

PI: R. R. Connelly Statistician BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided)*

The primary purpose of this project is to describe and evaluate the distribution of cancer occurrence in the United States in terms of age, sex, race, place, and time in order to identify subgroups of the population that offer possibilities for mortality reduction through intervention. Cancer incidence, mortality, and survival rates are analyzed using biostatistical techniques.

Kidney cancer cases ascertained among residents of Iowa by the SEER Program are being studied to determine if an increase in incidence can be correlated with the ethnicity of the population. The analysis involves monitoring the rate of disease in separate counties using the sets and cusum techniques.

In conjunction with investigators in the Environmental Epidemiology Branch, survival analyses of malignant mesothelioma cases ascertained through the SEER Program were completed. The findings suggest that age, gender and stage of disease should be carefully considered in designing and analyzing clinical trials for people with mesothelioma.

In collaboration with investigators in the Epidemiology and Biostatistics Program, age-period-cohort Poisson regression models are being used to analyze lung cancer mortality rates for World War I veterans.

A retrospective cohort study, done in collaboration with investigators in the Division of Cancer Etiology, was designed to detect the effects of cancer and its treatment on childhood patients who survived to adulthood. Among Wilms' tumor survivors, an excess of miscarriages and low birth weight babies were found compared to their sibling controls. In other analyses, survivors of central nervous system tumors showed significant education and marriage deficits compared to controls.

PHS 6040 (Rev. 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00113-05 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Cancer in Oriental Populations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

PI:	H. King	Research Sociologist	BMCCES, BB, DCPC, NCI
Others:	F. B. Locke	Statistician	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.0	1.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided.)*

Studies of Oriental populations represent the Division's continuing interest in the health risk among these minority groups for the mapping out of cancer prevention and control programs:

- A critical review of mortality/incidence statistics in the PRC is being conducted to ascertain their usefulness for analytic purposes, and for planning of future studies of cancer-related diseases.
- A time-trend study on cancer/non-cancer mortality was made of U.S. Chinese, by nativity, compared to the host (U.S. white) and homeland populations (Hong Kong, Singapore, Taiwan).
- Assembling mortality/incidence figures on Asian populations from various sources, we are establishing an international file of cancer/non-cancer causes since 1960. These Asian resource data, age-adjusted and age-specific rates, also include figures for U.S. and "homeland" populations.
- A companion mortality study of Chinese migrants to Taiwan and Singapore from Fujian to those who originated in Guangdong and settled in the U.S. and Hong Kong is being completed.
- Future plans include: a comprehensive analysis of mortality patterns of migrant Chinese and Japanese at geographic, generational, and temporal levels, including mortality transition among Chinese in Taiwan, and among U.S. Japanese; extension of nativity analyses of U.S. Asians to cancer incidence; and in cooperation with the Surveillance and Operations Research Branch to revise the SEER ethnic coding to separately identify Koreans, Vietnamese and Asian Indians.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00122-04 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Development of Cancer Control Epidemiologic Methods

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. L. Weed	Senior Staff Fellow	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

HPSB, DCPC, NCI (W. Mayer); NIOSH (T. Sinks); Fox Chase Cancer Ctr. (B. Trock); Univ. Michigan (J. Koopman); Office of Protection from Research Risks, NIH (C. McCarthy); Mt. Sinai Med. Ctr., (K. Ringen).

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The development of the methods of cancer control epidemiology has focused on these areas: 1) studies in causal and preventive inference, 2) studies in interactions, 3) the analysis of epidemiologic reasoning, 4) the ethics of prevention, and 5) design of cancer control research studies.

Criteria for causal and preventive inference have been improved. Previous criteria fall into two categories: those dependent upon the specific form of the hypothesis and those independent of the form of the hypothesis. Two general criteria replace all existing criteria: predictability and testability.

Studies of causal and preventive interactions have revealed that the links between biological and statistical models are necessary for scientific progress while the link between the discovery of interaction and its application requires examination of ethics. The use of the multiplicative model of preventive interaction (and the additive model of causal interaction) as thresholds for public health action are not justified on ethical grounds.

Research underway includes: 1) Application of general criteria of epidemiologic inference to determine status of hypothesis that dietary alcohol causes breast cancer and dietary fiber prevents colon cancer, 2) Predicting magnitudes of effects from the sufficient component causes model, and examining the role of magnitude of association in making inferences, 3) Application of a new causal theory (epigenesis theory) to the evaluation of causal and preventive interactions, 4) Application of a new method of epidemiologic reasoning (mega-analysis) to: the use of case-control methods for screening, the use of negative results in causal inference, the debate regarding the use of p-values, confidence limits, and p-value functions, the role of complexity in causal inference, and the links between scientific, technologic and ethical reasoning. 5) A critical study of the ethics of epidemiology in advising for or against preventive interventions, and 6) Defining criteria and issues of phase IV (defined population) studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00116-05 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Statistical Methodology Research

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. B. Green	Chief	CDTS, BB, DCPC, NCI
Others:	D. K. Corle	Computer Systems Analyst	CDTS, BB, DCPC, NCI
	B. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
	Y. Wax	Expert	CDTS, BB, DCPC, NCI
	R. Carroll	Guest Researcher	CDTS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

Information Management Services, Inc.

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.4	1.9	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to conduct research in statistical methods and computer techniques with particular emphasis on those appropriate for analyzing data from clinical, diagnostic, and prevention trials and epidemiologic studies of cancer. Many of the problems studied under this project arise from the consultative activities of the Section.

Important activities during the past year have included evaluation and application of methodology for the analysis of highly correlated dietary variables as risk factors for cancer, as well as accounting for the effect of measurement error (including correlated errors) and intra-individual variation in dietary data; studying approaches to doubly sampled survival data with informative censoring; and assessing power gains from matching on predictor variables in intervention studies, with emphasis on designs involving randomization of matched pairs of communities.

Previous work on an interactive computer program for calculating sample size has continued. Finally, the Section has continued to maintain and improve software for interactive analysis of complex medical data using sophisticated multiple regression techniques and survival analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00119-05 BB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Consultation on Clinical Trials and Other Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. B. Green	Chief	CDTS, BB, DCPC, NCI
Others:	D. K. Corle	Computer Systems Analyst	CDTS, BB, DCPC, NCI
	B. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
	Y. Wax	Expert	CDTS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*
Cancer Prevention Research Program, DCPC; Smoking, Tobacco, and Cancer Program, DCPC; Division of Cancer Treatment, NCI; Division of Cancer Biology and Diagnosis, NCI; Information Management Services, Inc.

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.3	1.9	0.4

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to provide consultation on statistical and epidemiological methodology in the design, interpretation, and evaluation of clinical trials of diagnosis, treatment, and prevention of cancer, and other studies requiring this kind of expertise. For some studies the Section provides full statistical support, including development of detailed study plans, assistance in the design of appropriate study forms, supervision of randomization (for trials) and collection, processing, and editing of data, performance of interim analyses during the progress of the study, preparation of progress reports, final analysis of study data, and collaboration in the preparation of scientific papers.

During the past year the Section has continued to collaborate extensively on the design and implementation of the Community Intervention Trial for Smoking Cessation; key activities during this year were the baseline survey and the randomization of communities. The Section has continued to provide full statistical support for the randomized clinical trials of treatment conducted by the Brain Tumor Cooperative Group.

Other important activities under this project include (1) multiple regression analyses of risk factors for breast cancer, using data from three major national studies; (2) studies of selenium pharmacokinetics (Z01 CN 00107-06 BB) applicable to possible prevention trials; (3) investigations to estimate population consumption of foods thought to be protective or harmful to cancer risk; (4) collaboration on a study of food purchasing behavior and consumer nutrition education; and (5) collaboration on workshops and planning sessions concerning the role of diet in gastric cancer and the design of intervention trials for this disease, including the role of intermediate endpoints.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00107-06 BB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Design and Analysis of Pharmacokinetic Studies of Selenium

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
Others:	L. A. Zech	Senior Scientist	LMMB, DCBD, NCI

COOPERATING UNITS *(if any)*

Laboratory of Mathematical Biology, DCBD
Cancer Prevention Studies Branch, DCPC

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.4	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Selenium is a possible cancer preventive agent, and is being considered for use in intervention trials. A study in collaboration with the Cancer Prevention Studies Branch (Z01 CN 00101-06 CPSB) is in progress which will provide information on the pharmacokinetics of selenium in its prototype forms -- sodium selenite (inorganic form) and selenomethionine (organic form). This information is unavailable for these agents in the dose currently considered optimal, and is necessary to the determination of time and manner of administration. Parameters such as percent absorption, maximum concentration, time to maximum concentration and mean residence times will be estimated for a single dose and compared in fasting and non-fasting subjects.

In order to interpret the study data more fully, development of integrated kinetic models, one for selenite and one for selenomethionine, is underway. Such models are useful in making inferences about drug metabolism and about the distribution of the drug in various body pools. A model of selenite has been developed based on pilot study data and tested on data from the main study. Various body pools have been hypothesized, and rates of exchange between them estimated, as well as mean residence times. Preliminary comparisons of rate constants for subjects when fasting and when non-fasting suggests that fasting status modulates the appearance of selenite in the plasma and that there is a greater first pass effect when the dose is given with food.

Another aspect of the project is an analysis of variations in total selenium levels in the plasma, urine and feces both within and between individuals. This information is important in deciding what measures can be used to determine selenium status.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00106-06 BB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*
Studies in Cancer Screening

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. C. Prorok	Chief	SS, BB, DCPC, NCI
Others:	R. J. Connor	Mathematical Statistician	SS, BB,DCPC, NCI
	S. G. Baker	Senior Staff Fellow	SS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

Centocor Co. (V. Zurawski), DuPont Co. (W. Vogler)

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Screening Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.2	0.8	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided.)*

Data from several cancer screening studies are being collected and analyzed to gain a better understanding of the impact and consequences of such screening in various population settings, and to develop new techniques for data analysis. Section staff are involved in various aspects of these studies, including design, monitoring and data analysis.

The data base from the HIP breast cancer screening trial was used to address several scientific and modeling issues. Issues under investigation include the magnitude and duration of benefit, age-specific effectiveness, and application to model development. Data from the NCI sponsored lung cancer screening trials were analyzed. Investigations included assessment of incidence, staging, survival and mortality information. Monitoring continues of a trial to evaluate testing for blood in the stool for the early detection of colorectal cancer.

Staff are also involved in several observational studies of screening procedures. In collaboration with investigators from the Centocor Company, the value of using the CA125 assay as a test for the early detection of ovarian cancer is being studied. Preliminary results indicate that the test may be useful in identifying a population of women at high risk for ovarian malignancy. Screening for bladder cancer in a high risk occupational cohort is under investigation in cooperation with DuPont Company staff. Data are being analyzed to relate disease characteristics and outcome to urine cytology and blood tests, smoking history and chemical exposure.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00105-06 BB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Research in Cancer Screening and Statistical Methodology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. C. Prorok	Chief	SS, BB, DCPC, NCI
Others:	R. J. Connor	Mathematical Statistician	SS, BB, DCPC, NCI
	S. G. Baker	Senior Staff Fellow	SS, BB, DCPC, NCI
	D. L. Weed	Senior Staff Fellow	BMCCES, BB, DCPC, NCI
	K. C. Chu	Health Science Administrator	CDB, CCOP, DCPC, NCI

COOPERATING UNITS *(if any)*

Cancer Detection Branch, CCOP, DCPC, NCI; Harvard School of Public Health (N.Laird); University of Erlangen-Nurenberg (K. Heidenberger).

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Screening Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892-4200

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	1.5	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews

☐ (b) Human tissues

☒ (c) Neither Analysis of data originally obtained from Human Subjects/Human Tissue

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The focus of this project is development and refinement of statistical procedures for the design and analysis of cancer screening and related studies. Problems under investigation include development and comparison of data analysis methods, assessment of case-control studies for screening evaluation, development of models of cancer screening, and approaches to the analysis of categorical data. Properties of case-control studies in the context of screening evaluation are being considered. Screening effect as estimated from a case-control study within a randomized trial was compared with the trial result as a standard, initially using data from the HIP study. Alternative definitions of cases, controls and exposure were assessed. A stage-shift cancer screening model was developed which uses the number of cancers diagnosed by stage in screened and control groups to estimate the number of cases shifted to earlier stages as a result of screening and the mortality impact. Application to the HIP data indicated that the bulk of the mortality reduction resulted from earlier detection of stage I and II cancers. A method called Periodic Screening Evaluation was created which uses data from individuals screened at different ages over a short term with no control group to estimate the impact of long term periodic screening starting at different ages. Research into surrogate endpoints which might be valid proxies for mortality in screening studies focused on stage shift, stage rate and survival variables. The most promising surrogate is the rate of advanced stage disease. Regression models for doubly sampled categorical data with nonignorable sampling mechanisms and partial validation were studied. These focus on the relation between covariates and true response in the categorical data setting where two samples are available, one containing data on covariates and a surrogate response, the other data on true response, surrogate response and perhaps covariates.

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